EXHIBIT 51

American Journal of Industrial Medicine 19:701–704 (1991)

RESEARCH ARTICLES

Translocation of Inhaled Asbestos Fibers From the Lung to Other Tissues

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To investigate translocation of asbestos fibers, tissue samples from 13 North American insulators were examined, using electron microscopy. Of the two major types of asbestos, chrysotile and amosite, chrysotile was found to be much more active in the translocation than amosite, being the fiber mainly detected in mesotheliomas and hyaline plaques.

Key words: chrysotile, amosite, lung tissue burden, mesothelioma, hyaline plaques

INTRODUCTION

Asbestos fibers are known to be durable and not easily digested or dissolved after being inhaled into the lung. Some are cleared from the lung [Wagner et al., 1974]; this clearance is greater for chrysotile than for amphiboles.

The fate of asbestos fibers cleared from the lung has not been completely explored. If they are totally cleared to outside the host's body, the risk of asbestos-related diseases will be correspondingly low although initial cellular and nuclear changes might have long-term consequences. However, such an optimistic assumption may not be entirely warranted, since translocation of intrapulmonary asbestos fibers (particularly chrysotile) from the lung into the parietal pleura has been indicated by the tissue burden studies of LeBouffant et al. [1973] and Sébastien et al. [1980]. Numerous short chrysotile fibers were found in pleural hyaline plaques in the former, and the latter detected asbestos fibers in both the lung and the fibrotic parietal pleura in a patient with asbestosis who had been exposed to both chrysotile and amphiboles. Long amphibole fibers predominated in the lung, while short chrysotile fibers were seen exclusively in the fibrotic parietal pleura.

We have also seen asbestos fibers in "Zuckerguss" (a type of peritoneal fibrosis, histologically identical to hyaline plaque) of the hepatic and splenic capsules obtained from people who had been occupationally exposed to both chrysotile and

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Accepted for publication September 24, 1990.

TABLE I. Demographic and Pathological Features in a Study of 13 North American Asbestos Insulation Workers

Case no.	Age at death	Sex	Smoking history[a]	Asbestos exposure: Age and year of onset	Asbestos exposure: Duration[b]	Diagnosis[c]	Pathological features[d]
1	67	M	No data	25 ('41)	42	Asb	IF (s)
2	54	M	No data	21 ('52)	34	Asb	IF (m)
3	58	M	40 PY	21 ('47)	37	Asb	IF (m), PC
4	63	M	100 PY	20 ('39)	44	Asb + LC	IF (s), Sc-C
5	62	M	15 PY	20 ('43)	41	Asb + LC	IF (s), Ad-C
6	70	M	25 PY	31 ('40)	40	Asb + LC	IF (s), Lc-C
7	52	M	No data	18 ('43)	34	Pl. Meso	IF (n)
8	67	M	No data	24 ('39)	44	Pl. Meso	IF (s)
9	55	M	Ex-smoker	27 ('48)	29	Pe. Meso	IF (m)
10	56	M	35 PY	24 ('50)	32	Pe. Meso	IF (s)
11	62	M	No data	24 ('36)	38	Pe. Meso	IF (s)
12	71	M	Non-smoker	18 ('30)	53	Pe. Meso	IF (m)
13	45	M	40 PY	19 ('54)	27	Pe. Meso	IF (s)

[a]PY, pack years.
[b]Years from first exposure to death.
[c]Asb, asbestosis; LC, lung cancer; Pl, pleura; Pe, peritoneum; Meso, mesothelioma.
[d]IF, interstitial fibrosis; (s), severe; (m), moderate, (n), none; PC, pancreas cancer, Lc-C, large cell carcinoma; Sc-C, small cell carcinoma.

amphibole asbestos (unpublished data). The asbestos fibers detected in "Zuckerguss" were overwhelmingly chrysotile.

Questions have been raised as to whether the translocation of inhaled asbestos fibers from the lung to the pleura and/or the peritoneum occurs commonly and whether chrysotile has a strong potential to translocate into these serosal tissues from the lung.

MATERIALS AND METHODS

To explore the problem, we have compared the type, number, and size distribution of asbestos fibers in lung parenchyma with those of fibers in tissues other than the lung parenchyma, such as lung cancer tissue (the primary site of bronchogenic carcinoma), fibrotic parietal pleura (mainly hyaline plaques), neoplastic pleura (the primary site of malignant pleural mesothelioma), and neoplastic peritoneum (malignant peritoneal mesothelioma). This is a preliminary report of the study; additional details will be reported [Kohyama and Suzuki, 1991].

Tissues were collected from 13 North American insulation workers. These 13 cases included three of asbestosis, three of lung cancer, two malignant pleural mesotheliomas, and five malignant peritoneal mesotheliomas. Table I shows age, sex, smoking history, history of exposure to asbestos, classification of the disease, and histopathologic findings. North American insulators are known to have been occupationally exposed to an admixture of chrysotile (mainly Canadian) and amosite (South African) [Selikoff et al., 1979]. It was noteworthy that, histologically, pulmonary asbestosis was seen in all but a single case (case 7: pleural mesothelioma).

Characterization of the asbestos was accomplished using analytical electron microscopy of digested bulk tissues obtained from various sites, such as the lung, pleura, and peritoneum, as described above.

RESULTS

Chrysotile (15–196 $\times$ 10^6/g dry lung; 63.1 $\times$ 10^6/g dry lung mean value) and amosite (7.27–415 $\times$ 10^6; 150.2 $\times$ 10^6 mean value) were the major asbestos types seen in the lung parenchyma of all 13 cases. Amphiboles other than amosite were also seen in the lung: crocidolite fibers were seen in the lung of 7 of the 13 cases but the numbers were much smaller (1.28–86.4 $\times$ 10^6; 11.4 $\times$ 10^6 mean value) than either chrysotile and amosite. A small number of anthophyllite fibers (2.83–3.50 $\times$ 10^6/g dry lung; 1.86 $\times$ 10^6 mean value) were identified in 3 of the 13 cases. A small number of tremolite or actinolite fibers were also seen in another three (3–11.3 $\times$ 10^6; 2.45 $\times$ 10^6 mean value).

The proportion of asbestos types seen in either the pleural tissue (hyaline plaques or primary pleural mesothelioma tissue) or peritoneal tissue (the primary peritoneal mesothelioma tissue) was very different from that seen in the lung. In the pleural tissue, (11 samples from 10 cases: 10 samples of hyaline plaques and 1 of the primary pleural mesothelioma), the number of intrapleural amosite fibers (dry weight) was dramatically less (0–6.81 $\times$ 10^6; 2.18 $\times$ 10^6/g, mean value) than the intrapleural chrysotile (12.1–89.7 $\times$ 10^6; 46.3 $\times$ 10^6/g, mean value). In the peritoneal tissue (six samples from five peritoneal mesothelioma tissues), amosite was 0–14.2 $\times$ 10^6 (3.05 $\times$ 10^6 mean value) and chrysotile was 12.5–89.6 $\times$ 10^6 (37.9 $\times$ 10^6 mean value). Unlike in the lung parenchyma, amphiboles other than amosite (crocidolite, anthophyllite, tremolite, and actinolite) were not detected in either the pleural or peritoneal tissues.

DISCUSSION

These findings indicate that: 1) inhaled asbestos fibers were translocated from the lung into the pleura and the peritoneum; and 2) the potential for translocation is different for chrysotile and amphibole asbestos fibers, chrysotile having a significantly greater tendency to translocate, compared with amosite.

The size distrubution (length and width) of the detected asbestos fibers was compared among three sites; lung (non-neoplastic lung parenchyma and the primary site of lung cancer); parietal pleura (hyaline plaques); and peritoneum (peritoneal mesothelioma tissue) in three cases (a lung cancer, a pleural mesothelioma, and a peritoneal mesothelioma). No significant differences of the size distribution of asbestos fibers were seen in the three tissues.

It was noteworthy that long (> 50 μm), and thick, (> 0.25 μm) asbestos fibers were rare in the lung, suggesting that such fibers do not easily reach the lung parenchyma through the respiratory tract.

CONCLUSIONS

The present study has led us to the following conclusions: 1) translocation of inhaled asbestos fibers from the lung to other organs, such as the pleura and the peritoneum, seemed to occur frequently among asbestos insulation workers, although

the route of the translocation has not been completely investigated; 2) in insulation workers (occupationally exposed to asbestos, mainly chrysotile and amosite), chrysotile seemed to be more actively cleared from the lung and translocated into extra pulmonary tissues, compared with amosite; 3) chrysotile fibers cleared from the lung were not later eliminated from the host. Biological effects of the translocated asbestos fibers may be significant, and translocated chrysotile fibers may play an important role in the induction of either malignant mesothelioma and/or hyaline plaques. The asbestos fibers detected in both were mainly chrysotile.

ACKNOWLEDGMENTS

We thank Dr. Irving J. Seilikoff for providing the material. The assistance of Richard Ashley, Anna Calderaro, and Steven R. Yuen is gratefully acknowledged.

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